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Introduction

Depression is one of the leading causes of disability globally (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). A great part of this burden is related to frequent relapses and chronic course, in that more than 50% of patients with a first episode of depression will go on to have a second episode, and approximately 80% of these will have further episodes (American Psychiatric Association, 2000). Therefore, prevention of relapses is an important component in the management of depression. Continuation of antidepressants is recognised to prevent relapses more effectively than placebo; nevertheless substantial proportions of patients experience relapses (Keller et al., 1998; McGrath et al., 2006; Fava et al., 2009). Identifying predictors of relapse could inform preventive strategies by differentiating those patients with a higher risk, and then monitoring and managing them more carefully.

Many studies have reported potential risk factors for depression relapse, mostly focusing on socio-demographic and clinical characteristics evaluated at the time of antidepressant initiation. From these studies, number of prior depressive episodes, severity of the index episode, and comorbid anxiety or substance use disorders have been relatively consistently identified as risk factors (Stewart et al., 1998; Nierenberg et al., 2004; Kessing 2004; Joliat et al., 2004; Katon et al., 2006). Other factors including age, sex, marital status, and socio-economic status have been less consistently reported (Hochstrasser et al., 2001; Birmaher et al., 2002; McGrath et al., 2006; Fava et al., 2009; Kornstein et al., 2014).

Almost all previous studies of relapse predictors have been designed in trials of antidepressant monotherapy compared to placebo for up to 12 weeks and have investigated relapse over 26–104 week follow-up periods (Berwian et al., 2016). Samples have also tended to comprise potentially highly selected recruited patients with major depressive disorder (MDD) with strict inclusion and exclusion criteria applied (Berwian et al., 2016), which may limit generalizability to standard clinical practice. Moreover, among patients with MDD who failed
to show an early response to initial antidepressant monotherapy within 2~4 weeks, there is accumuating evidence that stepwise pharmacotherapy, making clinical decisions every 2~4 weeks by using guidelines and rating scales to inform medication change or supplementation strategies, is associated with significantly better treatment outcomes compared to continuation of antidepressant monotherapy (Tadić et al., 2016; Guo et al., 2015; Han et al., 2018; Fabbri & Serretti, 2020). However, these studies of stepwise pharmacotherapy based on early clinical decision have, in turn, investigated only symptom remission status, and have not evaluated longer-term depression relapse or its predictors.

Using data from a naturalistic prospective study of Korean patients with depressive disorder, we have reported effects of stepwise pharmacotherapy based on early clinical decision on remission of depressive symptoms (Kim et al., 2020). By extending this cohort, we aimed to investigate predictors of depression relapse over a 24-month follow-up period.
**Methods**

**Study outline and design**

This study was carried out as a component of the MAKE Biomarker discovery for Enhancing antiDepressant Treatment Effect and Response (MAKE BETTER) programme. The present analysis focused on predictors of relapse rather than those of treatment response, which were the main objectives of this programme. Details of the study have been published as a design paper (Kang et al., 2018) and registered with cris.nih.go.kr (identifier: KCT0001332). To reflect the real-world treatment settings, participants were enrolled regardless of depression subtypes or physical comorbidity. Treatment interventions were also conducted in a naturalistic fashion in determining the type, dose, and regimen of antidepressant and other medications, considering patient preference as well as clinician decisions, but were guided by pre-planned measurements and time points. After a 3-week antidepressant monotherapy period, next-treatment steps with alternative strategies could be initiated every 3 weeks during the acute treatment phase (3, 6, 9, 12 weeks), and every 3 months during the continuation (6, 9, and 12 months) and maintenance (15, 18, 21, and 24 months) treatment phases. For those who responded to the 12-week acute treatment phase, relapse status was investigated from 6 months to 24 months. All data on socio-demographic and clinical characteristics at baseline, and treatment related variables at follow-ups were obtained using a structured clinical report form (CRF) by clinical research coordinators who were blind to treatment modalities. These staff were trained in CRF implementation and data collection methods by the research psychiatrists. Patients’ data were recorded on a CRF, registered in the website of the MAKE BETTER study (http://icreat.nih.go.kr/icreat/webapps/com/hismainweb/jsp/cdc_n2.live) within 3 days, and monitored by data management centre personnel. This study was approved by the Chonnam National University Hospital Institutional Review Board (CNUH 2012-014).
Participants

Patients with depressive disorders were consecutively recruited from March 2012 to April 2017 from those who had visited the outpatient psychiatric department of Chonnam National University Hospital. All inclusion instances represented new treatment episodes – i.e. taking newly initiated antidepressant treatment – whether depressive symptoms were first-onset or recurrent. Since the primary objective of the MAKE BETTER study was to discover predictive markers for antidepressant treatment response, all participants were enrolled, with their consent, in order to receive antidepressant-based treatment approaches only. Inclusion criteria were: i) aged older than 7 years; ii) diagnosed with MDD, dysthymic disorder, or depressive disorder not otherwise specified (NOS), using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), a structured diagnostic psychiatric interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (APA, 1994); iii) Hamilton Depression Rating Scale (HAMD), the 17 item unstructured with ratings only version, (Hamilton, 1960) score ≥ 14; iv) able to complete questionnaires, understand the objective of the study, and sign the informed consent form. Exclusion criteria were as follows: i) unstable or uncontrolled medical condition; ii) unable to complete the psychiatric assessment or comply with the medication regimen, due to a severe physical illness; iii) current or lifetime DSM-IV diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder NOS, or other psychotic disorder; iv) history of organic psychosis, epilepsy, or seizure disorder; v) history of anticonvulsant treatment; vi) hospitalization for any psychiatric diagnosis apart from depressive disorder (e.g., alcohol/drug dependence); vii) electroconvulsive therapy received for the current depressive episode; viii) pregnant or breastfeeding. All participants reviewed the consent form and written informed consent was obtained. For participants aged under 16, written consent was obtained from a parent or legal guardian, and written assent was obtained from the participant.
Baseline characteristics

Socio-demographic characteristics obtained comprised age, gender, year of formal education, marital status (currently married or not), cohabiting status (living alone or not), religion (religious observance or not), occupation (current employed status or not), and monthly income (above or below 2,000 USD). Clinical characteristics evaluated comprised diagnoses of depressive disorders as mentioned above with certain specifiers, age at onset and duration of illnesses, number of previous depressive episodes, duration of present episode, family history of depression, and number of concurrent physical disorders (applying a questionnaire enquiring about 15 different systems or disorders).

Assessment scales for investigating symptoms and function were administered. Depressive and anxiety symptoms were evaluated by the Hospital Anxiety Depression Scale-depression subscale (HADS-D) and anxiety subscale (HADS-A) (Zigmond and Snaith, 1983), respectively; quality of life by the EuroQol-5D (EQ-5D) (Rabin and Charro, 2001); functioning levels by the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994); number of stressful life events by the Life Experiences Survey (LES) (Sarason et al., 1978); subjective perception of stress by the Perceived Stress Scale (PSS) (Cohen et al., 1983); psychological resilience by the Connor-Davidson Resilience Scale (CDRS) (Connor & Davidson, 2003); social support deficits by the Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet et al., 1988); and screening for alcohol related problems by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). Higher scores on HADS-D, HADS-A, EQ-5D, LES, PSS, MSPSS, and AUDIT indicate more severe symptomatology, as do lower scores on SOFAS and CDRS.

Stepwise pharmacotherapy
Details of the overall treatment steps and strategies in this study have been previously published (Kim et al., 2020). Before treatment commencement, a comprehensive review was made of each patient’s clinical manifestation (e.g. presence of psychotic or anxiety symptoms), severity of illness, physical comorbidity and medication profile, and history of previous treatments. Minimal and maximal dosages of pharmacological agents were determined considering existing treatment guidelines (Anderson et al., 2008; Bauer et al., 2013). In the first treatment Step 1, patients received antidepressant monotherapy, taking into consideration these data and treatment guidelines (Bauer et al., 2013; Malhi et al., 2015; Kennedy et al., 2016) for 3 weeks. Antidepressants used were bupropion, desvenlafaxine, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. After Step 1 antidepressant monotherapy, next step pharmacotherapy could be administered every 3 weeks during the acute treatment phase and every 3 months during the continuation and maintenance treatment phase, whenever needed. At the end of each step, overall effectiveness and tolerability were reviewed before proceeding with measurement-based next-step treatments. In cases of insufficient improvement (a HAMD score reduction of <30% from the previous step) or intolerable side effects, patients were instructed to choose whether they would prefer to remain in the current step or enter next-step strategies with switching to other antidepressants (S), augmentation with drugs other than antidepressants (A), combination with other antidepressants (C), or multiple strategies (S+A; S+C; A+C; S+A+C). Patients were also allowed to receive next step treatment if they showed sufficient improvement (a HAMD score reduction of ≥30% from the previous step) and absent/tolerable side effects. For determining treatment strategies, each patient’s preference was given priority to maximize medication compliance and treatment outcomes. Antidepressants switched or combined were bupropion, desvenlafaxine, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Augmentation drugs were buspirone, lithium, triiodothyronine, and atypical antipsychotics.
including aripiprazole, risperidone, olanzapine, quetiapine, and ziprasidone. Since the number entered into Step 5 or above was small, treatment steps were classified into Step 1, 2, 3, and 4 (including Step 5+) in the analysis. Medication adherence was estimated based on the tablet counts at every visit and was defined as poor in cases with less than 50% intake (Haynes et al., 2002).

Definition of the relapse

Patients who responded to the 12-week acute treatment phase (HAMD < 14) were included for relapse analyses. They were divided into remission (HAMD < 8) and partial response (HAMD 8~13) groups according to HAMD scores at the 12-week point. Relapse status was estimated according to protocol from 12 week and at every 3 months thereafter up to 24 months with a 7-day allowable window for re-assessment. Relapse was defined as a HAMD score ≥ 14, consistent with other previous studies (Stewart et al., 1998; Rush et al., 2006). Time to first relapse from after the 12 week evaluation point was the main outcome measure.

Statistical Analysis

Baseline socio-demographic, clinical, and treatment related characteristics were compared by relapse status using t-tests or $\chi^2$ tests as appropriate. Characteristics significantly associated with relapse ($P<0.05$) were entered into Cox proportional hazards models to identify independent predictors. In the model 1, only the baseline socio-demographic and clinical characteristics were entered simultaneously, consistent with the previous studies (Keller et al., 1998; McGrath et al., 2006; Fava et al., 2009; Akechi et al., 2019). In the model 2, treatment related characteristics were added to the model 1 to investigate the confounding effects of treatment. Since the 12-week remission was more frequently achieved with increasing treatment steps in this patients (Kim et al., 2020), we evaluated further whether the stepwise
pharmacotherapy regime was associated with relapse. Treatment steps (Step 1, 2, 3, and 4) administered at the 12 week evaluation point were used in the analysis. Baseline and treatment data were compared between the four treatment steps using analysis of variance or \( \chi^2 \) tests with post-hoc Scheffe’s tests, or with individual pairwise post-hoc comparisons as appropriate. Kaplan–Meier curves were constructed and the cumulative proportion of relapse by treatment steps was compared using the log-rank tests. Cox proportional hazards models were used to assess the time to relapse after adjustment for the potential covariates, shown significant associations with treatment step groups (P<0.05). Most previous studies included only patients who had achieved full remission (Keller et al., 1998; McGrath et al., 2006; Fava et al., 2009; Kornstein et al., 2014; Akechi et al., 2019); therefore, to compare the findings with those studies, additional sensitivity analyses were carried out restricting to those with remission at the 12-week acute treatment phase. Statistical analyses were carried out using the SPSS 21.0 and STATA 12.0 software.
Results

Recruitment and flow

Patient recruitment and flow are described in Figure 1. Of 1262 patients evaluated at baseline, 1246 (98.7%) were followed at least once during the 12-week acute treatment phase. Reasons for drop-out were lack of treatment effect (N=7) and loss to follow-up (N=9). There were no statistical differences in any baseline characteristic between the 1246 patients included and the 16 not followed (all P>0.6). At the 12-week assessment point, 309 (24.8%) patients scored 14 or over on HAMD, and the remaining 937 scored less than 14 on HAMD [540 (43.3%) in remission and 397 (31.9%) with partial response]. Significant group differences between patients with lack of response and those with remission or partial response were found in age, marital and employed status, age of onset, number of depressive episodes and physical disorders, scores on HADS-D, HADS-A, EQ-5D, SOFAS, LES, PSS, CDRS, and MSPSS, and treatment step (eTable 1). After the acute treatment phase, 816 (87.1%) of these 937 patients were evaluated at least once during the 24-month follow-up period, and comprised the sample for the analyses presented here. Reasons for drop-out at this stage were lack of treatment effect (N=78), transfer to other hospital (N=9), intolerable side effects (N=6), poor physical condition (N=3), and loss to follow-up (N=25). Attrition at 12 months was significantly associated with unemployed status and higher EQ-5D scores at baseline.

Unadjusted associations with relapse

The cumulative relapse rate up to 24 months was 41.9% (342 of 816 patients). Baseline and treatment related characteristics are compared by relapse status in Table 1. Relapse was significantly associated with higher number of previous depressive episodes, higher baseline scores on HADS-D, HADS-A, EQ-5D, and PSS, lower score on SOFAS, higher number of treatment steps, and poor medication adherence.
Predictors of relapse

Predictors of relapse in Cox proportional hazards models are summarized in Table 2. In the model 1 with baseline socio-demographic and clinical characteristics, the factors that retained a significant association with relapse were higher number of previous depressive episodes and higher score on HADS-A. In the model 2 with adding treatment related characteristics, the strengths of the associations with higher number of previous depressive episodes and higher score on HADS-A were weakened but remained significant. Furthermore, significant associations were additionally found with higher number of treatment steps and poor medication adherence.

Relapse by treatment steps

At the 12 week evaluation point, 283 (34.7%) patients had received Step 1 antidepressant monotherapy treatment, 274 (32.6%) had received Step 2 treatment, 171 (20.9%) Step 3 treatment, and 88 (10.8%) Step 4 treatment. Baseline and treatment related characteristics between the four treatment step groups are compared in eTable 2. Significant group differences were found in diagnosis of depressive disorder, atypical features, scores on HADS-A, EQ-5D, PSS, and CDRS, 12-week treatment outcomes, and poor medication adherence. There was a general pattern of worse clinical presentations at baseline but better treatment outcomes associated with higher treatment steps. In post-hoc comparisons, patients who received Step 4 and/or Step 3 treatment were significantly more likely to have atypical features, and higher scores on HADS-A, EQ-5D, and PSS, but lower scores on CDRS compared to those who received Step 1. However, patients who received higher treatment steps were significantly more likely to have remission at the 12-week point and better medication adherence. Cumulative incidences of relapse in the four treatment steps are illustrated in Figure 2 [Step 1: 38.9%
Significant group differences were found across the four treatment steps (log-rank P<0.001).

Adjusted associations of treatment steps with relapse are described in Table 3. Treatment Step 4 had significantly higher hazards of relapse compared to treatment Step 1, 2, and 3; while there were no differences between treatment Steps 1, 2, and 3 after adjustment for diagnosis of depressive disorder, atypical features, number of depressive episodes, scores on HADS-A, EQ-5D, PSS, and CDRS, 12-week treatment outcomes, and poor medication adherence.

**Relapse outcomes restricted to those with remission at 12 weeks**

The same analyses above were repeated restricting the analysed sample to patients with remission in the 12-week acute treatment phase (N=485). In the unadjusted analysis, relapse was significantly associated with earlier age at onset, longer duration of illness, higher number of previous depressive episodes, higher scores on HADS-D, HADS-A, and EQ-5D, higher treatment steps, and poor medication adherence (eTable 3). Predictors of relapse in Cox proportional hazards models were higher number of previous depressive episodes, higher score on HADS-A, higher number of treatment steps, and poor medication adherence, i.e. the same results as observed in the total sample (eTable 4).
Discussion

In this study of stepwise pharmacotherapy for depressive disorders in an outpatient clinical setting and following a naturalistic and flexible treatment protocol, two baseline factors (higher number of previous depressive episodes and higher score on HADS-A) and two treatment related factors (higher number of treatment steps and poor medication adherence) were identified as predictors of relapse up to the 24-month follow-up point after the treatment initiation. In particular, treatment Step 4 was significantly associated with relapse compared to treatment Step 1, 2, and 3 even after adjustment for relevant covariates. The results were same regardless of the level of remission status evaluated at the end of the 12-week acute treatment phase.

The most distinct aspect of the study design for this cohort was that treatment steps could be advanced every 3 weeks with a range of treatment strategies possible during the 12-week acute treatment phase, compared to other studies which have restricted samples to those receiving only antidepressant monotherapy (Keller et al., 1998; Stewart et al., 1998; Hochstrasser et al., 2001; McGrath et al., 2006; Fava et al., 2009; Nierenberg et al., 2004; Iovieno et al., 2010; Akechi et al., 2019). This study design was chosen because of individual reports on benefits of early clinical decision-making (Tadić et al., 2016; Guo et al., 2015) and of alternative treatment strategies (Blier et al., 2010; Zhou et al., 2015) in the treatment of MDD. However, despite such differences in study design, three of four identified factors (higher number of previous depressive episodes, higher anxiety at baseline, and poor medication adherence) were similar between the present study and others.

Several studies have reported significant associations between prior number of depressive episodes and depression recurrence, even after adjustment for age of onset (Gonzales et al., 1985; O’Leary & Lee 1996; Levinson et al., 2000; American Psychiatric Association, 2000). This association is potentially explained by the kindling hypothesis in that
the onset of depressive episodes might become increasingly autonomous over the course of illness (Kendler et al., 2000). More severe symptoms at baseline have fairly consistently been associated with depression relapse (O’Leary et al., 2000; Kessing, 2004). In the present study, multi-faceted evaluations were made using various assessment scales for baseline symptom severity including depression, anxiety, quality of life, and functioning. All these symptom domains were significantly associated with depression relapse in the unadjusted analysis. However, only anxiety symptoms as evaluated by the HADS-A were identified as a significant predictor of relapse in the multivariate analysis. This finding was in keeping with previous observations on the significant associations between comorbid anxiety and depression relapse (Segal et al., 2003; Wilhelm et al., 1999; Joliat et al., 2004).

In the present study, the group with poor medication adherence (drug intake less than 50%) had 12% higher rates of relapse than the remainder of the sample. This finding should be interpreted cautiously because there might have been other unmeasured characteristics of those with lower adherence that might have influenced relapse risk. However, it was consistent with those from previous studies using placebo controls, have reported that depression relapse is 18–27% more frequent in the placebo than antidepressant-receiving group (Keller et al., 1998; Hochstrasser et al., 2001; McGrath et al., 2006; Fava et al., 2009).

A particular finding of the present study was that treatment Step 4 was significantly associated with relapse compared to treatment Step 1, 2, and 3. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, relapse was significantly more frequent with increasing treatment steps (from step 1 to step 4) (Rush et al., 2006), while only the treatment Step 4 was significantly different from other steps in our study. However, the STAR*D study design was different to ours in that the duration of every treatment step was 13 weeks, and therefore the total time up to the end of their treatment step 4 was 52 weeks. Our finding was unexpected since this group was associated with more frequent remission status,
as with Step 2 and 3, compared to treatment Step 1 at the end of acute treatment phase, and was associated with better medication adherence compared to treatment Step 1 and 2 during the treatment period (see eTable 1). Several explanations are possible. First, the patients included in the treatment Step 4 had unfavourable clinical presentations compared to others at baseline (see eTable 1), which have been associated with worse long-term treatment outcomes including relapse (Berwian, et al., 2016; Akechi et al., 2019). Second, these patients might have unfavourable biological predispositions for treatment resistance (Berwian et al., 2016; Kennis et al., 2019). Third, the potential iatrogenic effects of previously administered therapies from treatment Step 1 to Step 3 might underlie the unfavorable modifications in the disease course and treatment responsiveness (Fava et al., 2020). Similarly, the present and the STAR*D observations can also be interpreted in light of the oppositional model of tolerance in that pharmacological manipulations, either by switching or augmentation in the earlier treatment steps may propel depressive illness into a refractory phase, characterized by low remission, high relapse, and high intolerance in the later treatment steps (Fava & Cosci, 2019). Summing up, patients receiving Step 4 were an at-risk group for relapse, even though they showed response by 12 weeks to the given pharmacological strategy.

We conducted an additional analysis restricting to patients with remission at the end of the acute treatment phase in order to compare our findings more directly with those of previous studies using this inclusion criterion (Keller et al., 1998; McGrath et al., 2006; Fava et al., 2009; Kornstein et al., 2014; Akechi et al., 2019); however, we found that findings did not differ from the primary analysis, with the same four predictors extracted. Therefore predictors of depression relapse appeared to be independent of inclusion or not of partial responders although this result needs to be confirmed in future randomised trials.

Strengths of the study were that the sample size was larger and the follow-up period was longer than previous studies on this issue (Keller et al., 1998; Stewart et al., 1998;
Hochstrasser et al., 2001; McGrath et al., 2006; Fava et al., 2009; Nierenberg et al., 2004; Iovieno et al., 2010; Akechi et al., 2019). Participants were evaluated with a structured research protocol and well-recognized and standardized scales. As stated above, we believe this study to be the first to report on relapse predictors in the context of stepwise pharmacotherapy based on consecutive early clinical decision-making, and then to find that treatment Step 4 or above was associated with higher relapse rates.

Several limitations and considerations should also be borne in mind. A major limitation was that withdrawal syndromes after discontinuing psychotropic drugs, known to confound the determination of relapse (Baldessarini & Tondo, 2019; Cohen & Recalt, 2019) were not evaluated. The drug switching strategy and frequent poor medication adherence observed in our study might have given rise to withdrawal syndromes (Cosci and Chouinard, 2020), and could therefore have affected the observed findings. Second, the naturalistic design was both a strength and potential limitation. The broad inclusion and minimal exclusion criteria for recruitment, and the absence of limitations placed on treatment were designed to reflect real clinical situations as closely as possible and maximize generalizability to clinical practice. However, clinical heterogeneity at baseline such as comorbidities of psychiatric and physical disorders, and the usage of substances and other psychotropics might affect the observed results. Moreover, because the treatment modality was determined by patient preference guided by the treating clinician rather than by a predetermined protocol, inter-clinician variability might affect observed outcomes. Third, patients were unevenly distributed across the treatment steps (fewer patients in higher steps), which might attenuate statistical power and reduce generalisability. However, these phenomena were also observed in the STAR*D study, in that participants were reduced with higher treatment levels (Rush et al., 2006). Fourth, individual outcomes by each antidepressant and by each co-administered drug were not compared due to the use of too many separate strategies, although it is recognised that there are differences.
between drug regimens for treating depression (Cipriani et al., 2018). The fifth issue relates to follow-up rates over the treatment period. In the acute treatment phase, the follow-up rates were reasonable and there was no significant difference between those followed up and not. However, the follow-up rates were obviously reduced during the continuation and maintenance treatment phases, although were similar to those observed in the STAR*D one-year follow-up (Rush et al., 2006), and those lost to follow-up were more likely to have markers of poor prognosis at baseline such as unemployed status and higher EQ-5D scores, which might obscure observed findings. Sixth, the sample included not only participants with MDD but also those with dysthymic disorder or depressive disorder NOS, while previous research in this field has tended to focus on patients with MDD. However, the same inclusion criterion for depression severity (HAMD score ≥ 14) was applied regardless of diagnosis, and there were no significant differences in the proportions with MDD according to relapse status or between the treatment steps. Seventh, the unstructured version of HAMD, the information might be exclusively dependent on expertise and clinical judgment of raters (Carrozzino et al., 2020), was used in the study. Eighth, recruitment was carried out at a single site, which may limit the generalizability of the present findings, although a single centre study has potential strengths in terms of consistency in evaluation and treatment. Finally, no attempt was made to investigate the effect of non-pharmacologic treatment, which are evidence based treatment for depression including psychotherapy (Parikh et al., 2016) and physical exercise (Kvam et al., 2016) during the follow-up period, although within the Korean healthcare system this would be relatively uncommon.
Conclusion

The individual and healthcare impacts of depressive disorders are compounded by frequent relapses. We found that previously reported depression relapse predictors from placebo-controlled antidepressant monotherapy trials were replicated in real world clinical practice with stepwise pharmacotherapy based on early clinical decision making. They were also replicated in the broader spectrum of depressive disorders seen in routine clinical practice, and in patients with partial response as well as those with remission at the end of the acute treatment phase. Particular attention is warranted in patients receiving higher numbers of treatment augmentations and/or changes in order to achieve response, regardless of the level of remission achieved in the acute stage. Our findings have potential generalisability to the routine outpatient treatment of depressive disorders, since these were drawn from a naturalistic prospective design, maximising resemblance to real world clinical situations. However, it should be borne in mind that important issues such as drug withdrawal syndromes, iatrogenic effects, and the oppositional model of tolerance could confound the present findings with the particular treatment steps and strategies. Future studies considering these issues with evaluations in multi-site and multi-nation are needed.
Statement of Ethics

All patients gave written informed consent to participate in the study and use their data. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008 and approved by the Ethics Commission of the Chonnam National University Hospital Institutional Review Board (CNUH 2012-014) as it uses de-identified data. It was registered at cris.nih.go.kr (identifier: KCT0001332).
References


Figure 1. Patient recruitment and flow
Figure 2. Cumulative incidences of relapse according to the four treatment steps